REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

II. Status of the Claims

No claims are amended. Claims 1-27, 41, and 46 were cancelled by way of Applicants' previous responses. The present amendment cancels claims 47 to 50 for the sole purpose of expediting prosecution. Claims 28-40, 42-45, and 51-59 are therefore pending.

An issue underlying the prior art rejections discussed below is the PTO's contention that the claims lack support under 35 U.S.C. § 112, first paragraph, in Application Serial No. 08/394,103 ("the '103 application"), to which this application claims the benefit of priority. *See* Office Action at page 3, second paragraph. Specifically, the PTO requested Applicants to identify such support for "claims 10-40, 42-45, and 47-59." *Id.* In this regard, Applicants believe that the PTO's request does not apply to cancelled claims 10-27.

Applicants previously identified each passage of the '103 application that supports every element of independent claim 28. *See* Applicants' Response, dated February 4, 2004, at page 10 (Table). Based upon the PTO's present commentary, however, it appears that some confusion exists as to which specification text gives rise to this support. Applicants affirm that the cited passages refer to the '103 application text. For the PTO's convenience, and in a good faith effort to comply with the PTO's request for a showing of support (Office Action at page 3, second paragraph), Applicants present the following chart showing explicit support in the '103 application for the dependent claims:

Claim	Exemplary Support in '103 Application
29-31	"the particles have a weight average particle size of less than about 400 nm . . ."; "less than about 300 nm . . ."; "less than about 100 nm . . ." (Page 22, lines 26-35)
32	"Representative examples of surface modifiers include gelatin . . ." (Page 8, line 13 through page 13, line 6)
33	"Two or more surface modifiers can be used in combination." (Page 10, lines 26-27)

Claim	Exemplary Support in '103 Application
34-36	"The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably is 1-75%, more preferably 20-60%, by weight based on the total combined weight of the therapeutic agent or diagnostic agent and surface modifier." (Page 14, lines 3-9).
37	"Suitable therapeutic or diagnostic agents can be selected from a variety of known classes of therapeutic or diagnostic agents including, for example, analgesics . . ." (Page 6, line 10 through page 8, line 5)
38	"Example 1 . . . Beclomethasone dipropionate . . ." (Page 25, line 11 *et seq.*)
39, 40	"The concentration of the therapeutic agent or diagnostic agent in the liquid medium can vary from about 0.1-60%, and preferably is from 5-30% (w/w)." (Page 13, line 33 through page 14, line 1)
42	"Compressor driven nebulizers incorporate jet technology and use compressed air to generate the aerosol." (Page 5, lines 8-10)
43	"Ultrasonic nebulizers deliver high medication output . . ." (Page 5, lines 16-17).
44	"The aerosols of the present invention are particularly useful in the treatment of respiratory related illnesses such as asthmas, emphysema, respiratoy distress syndrome, chronic bronchitis, cystic fibrosis and acquired immune deficiency syndrome including AIDs related pneumonia." (Page 4, lines 22-27)
45	"liquid propellant containing the nanoparticulate dispersion is released . . ." (Page 5, lines 1-2)
51	"at least 90% of the particles have a weight average particle size of less than about 400 nm . . ." (Page 22, lines28-30)
52	"at least 95% . . . of the particles have a particle size less than the effective average . . ." (Page 23, lines 1-3)
53	"at least 99% of the particles have a particle size less than the effective average . . ." (Page 23, lines 1-3)
54	"the effective average particle size is less than about 300 nm . . ." (Page 22, lines 31-32)
55	"at least 95% . . . of the particles have a particle size less than the effective average . . ." (Page 23, lines 1-3)
56	"at least 99% of the particles have a particle size less than the effective average . . ." (Page 23, lines 1-3)
57	"an effective average particle size of less than about 100 nm has been achieved." (Page 22, lines 33-35)
58	"at least 95% . . . of the particles have a particle size less than the effective average . . ." (Page 23, lines 1-3)
59	"at least 99% of the particles have a particle size less than the effective average . . ." (Page 23, lines 1-3)

III. The Office Action

Applicants gratefully acknowledge the PTO's withdrawing the previous § 112, first paragraph, and obviousness-type double patenting rejections. Because the PTO has maintained the prior art rejection and has lodged one anew, no claims are allowable at present. Applicants now take up these issues in the order presented in the Office Action.

A. Priority

Despite Applicants' previous arguments, the PTO has repeatedly denied Applicants' claim to the benefit of domestic priority for an alleged want of written description in Application Serial No. 08/394,103. Office Action at page 3. In this context, Applicants recognize that the PTO's denial pertains to the extent that Wiedmann and Wood, discussed below, are available as prior art.

Applicants showed previously that the '103 application fully describes the subject matter of independent claim 28. *See* Applicants' Response, dated February 4, 2004, at pages 10-12. Additionally, the chart above should remove all doubt that the dependent claims are also fully supported in the '103 application. Applicants therefore respectfully submit that the present application complies with the strictures of the written description requirement, 35 U.S.C. § 112, first paragraph, and therefore should enjoy the benefit of the claim to priority. Accordingly, Applicants courteously request the PTO to acknowledge Applicants' proper claim to benefit of priority.

B. Rejections of Claims Under 35 U.S.C. § 103

1. James and Liversidge

a. The PTO's Ground for Rejection

Claims 28-40, 42-45, and 47-59 were rejected as being allegedly unpatentable over the newly cited *AIDS Treatment News No. 074* (February 10, 1989) by John S. James ("James") and previously cited U.S. Pat. No. 5,145,684 to Liversidge et al. ("Liversidge"). Office Action at page 4. According to the PTO, Liversidge teaches: (1) that air jet milling techniques provide particles ranging from 1 to 50 μm and (2) crystalline drug particles measuring less than 400 nm and having a surface modifier adsorbed thereto. The PTO recognizes that Liversidge "does not have aerosols." *Id.* The PTO relies upon James for its disclosure of pentamidine aerosols, which allegedly are used for the prevention of pneumocystis. While the PTO's analysis does not state the manner and reason(s) by which James

and Liversidge could or would have been combined, it nonetheless concludes that the invention would have been obvious to a person of ordinary skill in the art at the time the claimed invention was made in light of the cited combination. Applicants respectfully traverse the rejection.

b. There Is No Motivation to Combine the References

There is no suggestion whatsoever in the cited references, nor is one proffered by the PTO, for one of ordinary skill in the art to have combined Liversidge and James to arrive at the claimed method.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion of motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143.

Liversidge teaches certain nanoparticulate compositions and James teaches a pentamidine aerosol. As noted above and in the Office Action, Liversidge does not suggest the delivery of nanoparticulate compositions in an aerosol. Likewise, James does not teach or suggest aerosol compositions of nanoparticulate active agents, and the reference does not suggest that it would be desirable to do so. Thus the references, alone or in combination with each other, provide no suggestion or motivation whatsoever to combine the nanoparticulate compositions disclosed by Liversidge with the aerosol disclosed by James.

Applicants have argued extensively why "the knowledge generally available to one of ordinary skill in the art" at the time the claimed invention was made would have mitigated against making the combination urged by the PTO. *See* Applicants' Response, dated December 2, 2002, at pages 8-9. This knowledge includes, for example:

1. Aerosolization can produce unpredictable and inefficient delivery of poorly soluble particles.

2. Aerosolization of a poorly soluble active agent combined with a surface modifier is difficult or impossible.

3. A poorly soluble active agent and surface modifier composition is not suitable for respiratory delivery.

Id. In summary, the knowledge that was available to a person of ordinary skill in the art at the time the claimed invention was made would have *taught away* from Applicants' claimed invention. Consequently, neither the cited references themselves nor the general knowledge in the art provide the requisite motivation to combine Liversidge and James to obtain the claimed invention.

The cited art additionally teaches away from Applicants' claimed invention because active agent disclosed by James is water-soluble and therefore does not warrant the use of any novel dosage form such as nanoparticulate active agent formulations. Solubility of active agents greatly affects drug delivery, bioavailability, and overall efficacy of the active agents. Active agents that are water-soluble do not require special dosage forms because the active agents will dissolve readily in the water-based human body. By contrast, poorly water-soluble active agents generally require the use of solvents, which may give rise to unwanted side effects, and/or special dosage forms to obtain suitable bioavailability.

Here, James discloses pentamidine, which is commercially available as its *water-soluble* isethionate salt in the art-recognized formulation Nebupent® (see Exhibit A). By contrast, the present claims recite an active agent that is *poorly soluble in water*. Moreover, neither James nor Liversidge teach or suggest that *water-soluble* and *poorly water-soluble* active agents are or even could be interchangeable in the context of aerosol compositions. A person of ordinary skill in the art therefore would not have been motivated to supplant the water-soluble active agent in the aerosol disclosed by James by a nanoparticulate formulation of a poorly water-soluble active agent as taught by Liversidge because that person would not have expected an efficacious aerosol to result.

The PTO twice emphasized that the claimed invention would have been obvious. Office Action at pages 2 and 4. But nowhere in the PTO's analysis is it discussed how a person of ordinary skill in the art would have combined Liversidge and James to obtain the claimed invention, and why that person would have been motivated to do so. Rather, the PTO appears to affirm Applicants' remarks above: there is no motivation to combine. Because the PTO's obviousness determination lacks this requisite element, which for the reasons discussed above would not exist anyway, Applicants' respectfully submit that the claimed invention is not *prima facie* obvious over Liversidge and James. Accordingly, Applicants courteously request the PTO to reconsider and withdraw this rejection.

2. Wiedmann, Wood, and Liversidge

a. The PTO's Ground for Rejection

Claims 28-40, 42-45, and 47-59 stand rejected as being allegedly unpatentable over U.S. Pat. No. 5,747,001 to Wiedmann et al. ("Wiedmann"), U.S. Pat. No. 6,264,922 to Wood et al. ("Wood") and Liversidge. Office Action at page 5. In maintaining this rejection, the PTO reiterated its denial of Applicants' claim to the benefit of priority of the '103 application. *Id.* at page 3. Specifically, the PTO stated that "priority not [*sic*] granted because the subject matter in this application is different from the subject matter in 08/394103." *Id.* (emphasis in original). Applicants respectfully traverse this rejection.

b. Wiedmann and Wood Are Not Available as Prior Art Against the Claimed Invention

Applicants understand that in view of their previous arguments and the PTO's present commentary, the PTO would not dispute that Wiedmann and Wood are unavailable as prior art should the PTO grant Applicants' priority claim. In this regard, Applicants showed in the chart above that the '103 application fully describes all of the claimed subject matter. Applicants therefore submit that they properly claim priority as of February 24, 1995. Because Wiedmann and Wood were each filed on February 25, 1995, these references are not available as prior art against the claimed invention. For the reasons discussed above and previously by Applicants, Liversidge alone does not teach or suggest the claimed invention. Accordingly, Applicants respectfully submit that this rejection is now moot and request the PTO to reconsider and withdraw this rejection.

IV. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if she feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date July 22, 2004

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

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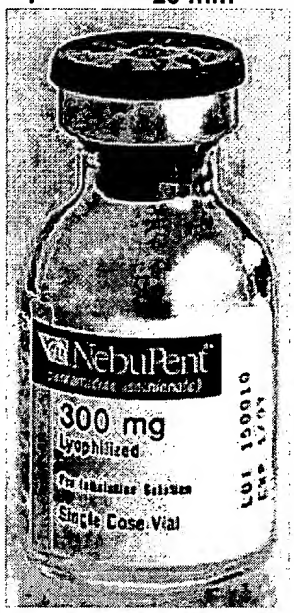

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